Armed Forces College of Medicine

AFCM

Tumor Immunology

Marwa Saad MD

Prof. of Medical Microbiology & Immunology

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this session the student will be able to:

1. Define tumor antigens and outline examples

2. Outline immune surveillance theory

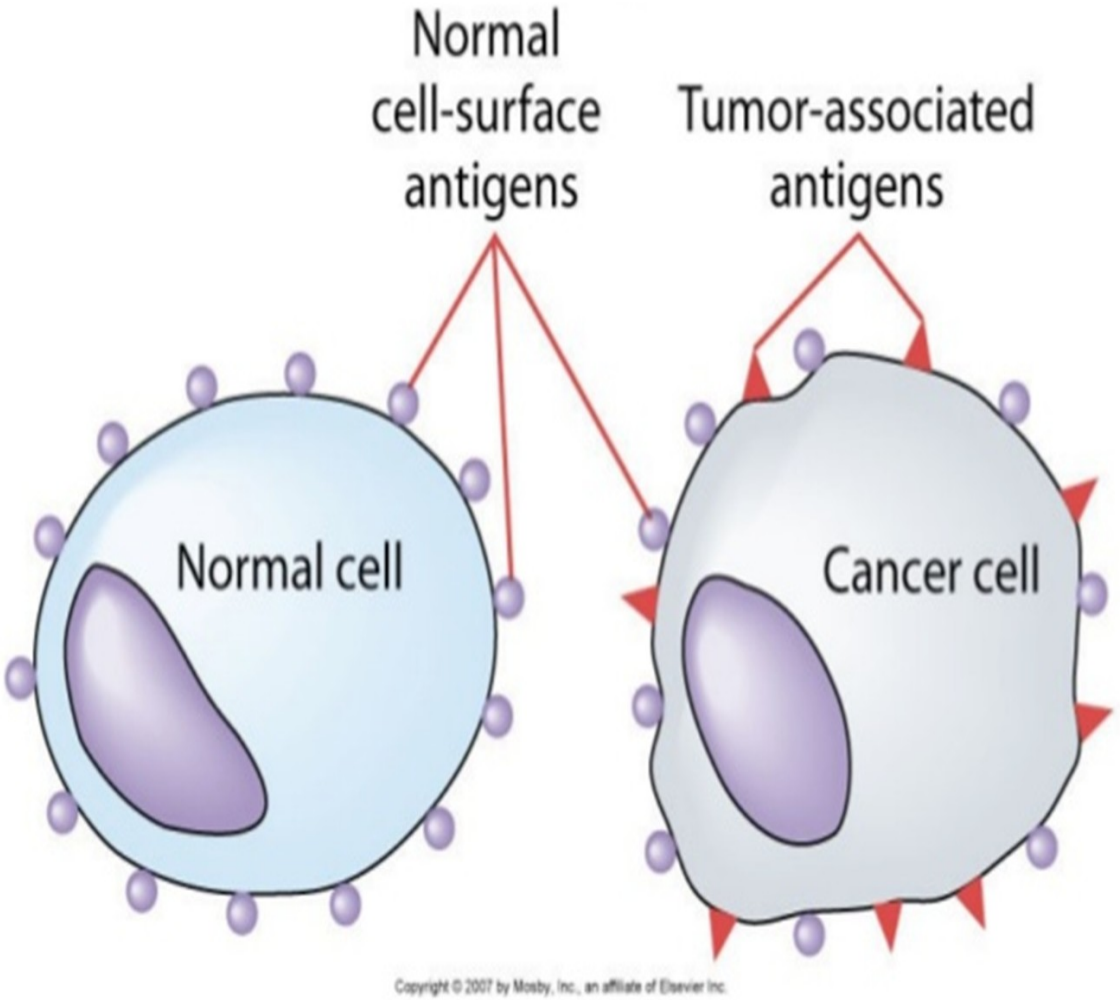
3. Mention the diagnostic and prognostic role of tumor markers .

4. Explain mechanisms by which tumors evade the immune response of the host

5. Identify the approaches for tumor immune therapy

Tumor Antigens

In the course of neoplastic transformation, new antigens develop at the cell surface, and the host recognizes such cells as "nonself."



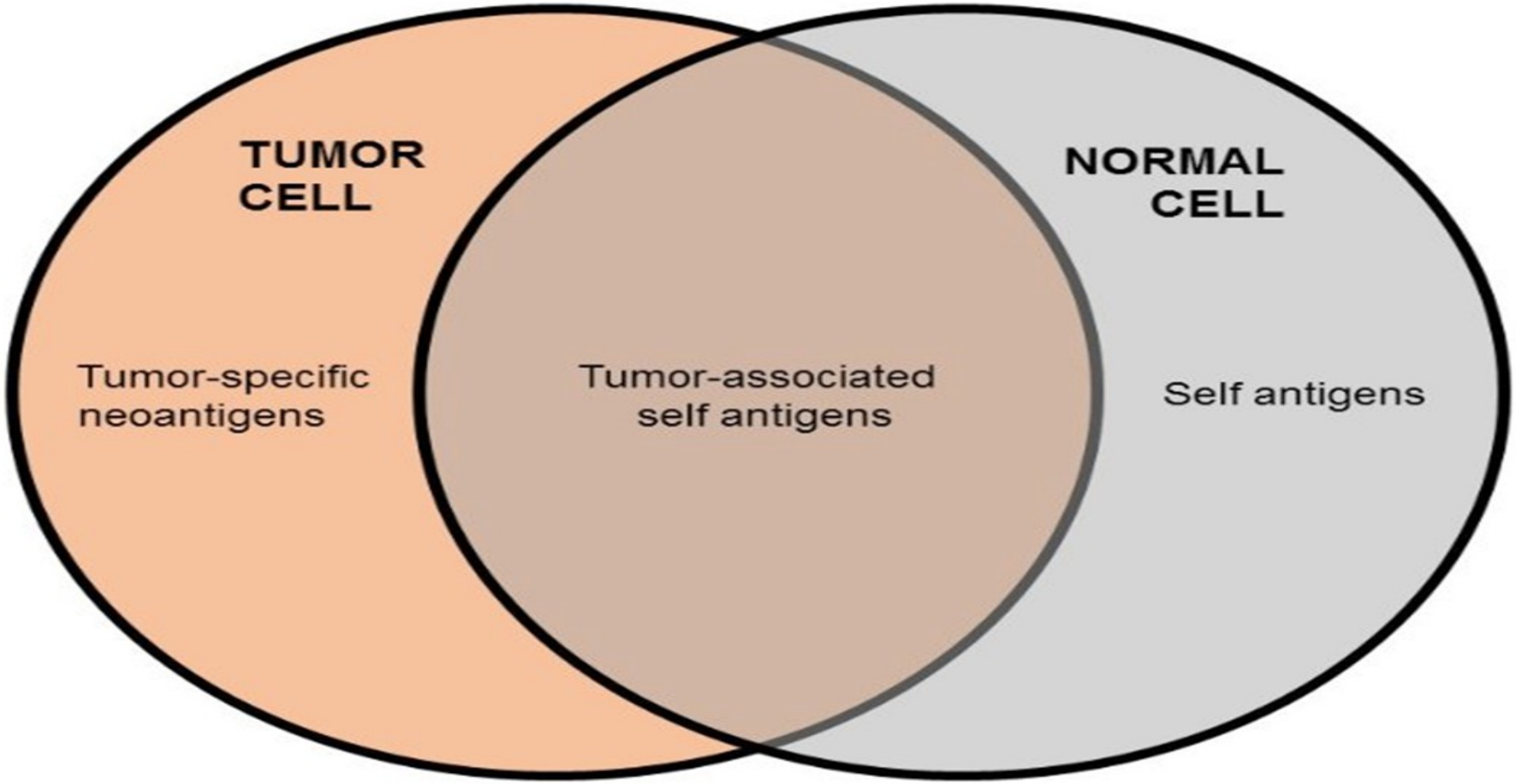
Tumor Antigens

- **I. according to pattern of expression:**

A. Antigens that are expressed on tumor cells but not on normal cells are called **tumor specific antigens**; some of these antigens are unique to individual tumors, whereas others are shared among tumors of the same type.

B. Tumor antigens that are also expressed on normal cells are called **tumor-associated antigens;** in most cases, these antigens are normal cellular constituents whose expression is aberrant or dysregulated in tumors.

Tumor Antigens



Tumor Antigens

II. According to molecular structure:

The modern classification of tumor antigens is based on the molecular structure and source of antigens expressed by tumor cells that stimulate T cell or antibody responses in their hosts.

Tumor Antigens

A. Tumor specific Antigens

Products of mutated:

Protooncogene /Tumor suppressor gene

Products of oncogenic viruses:

EBV HHV8 HPV

Tumor Antigens

B. Tumor non specific Antigens: Oncofetal antigens

Genes encoding these proteins are:

Expressed during fetal life with malignant tumors

Silenced during development

Re-expressed

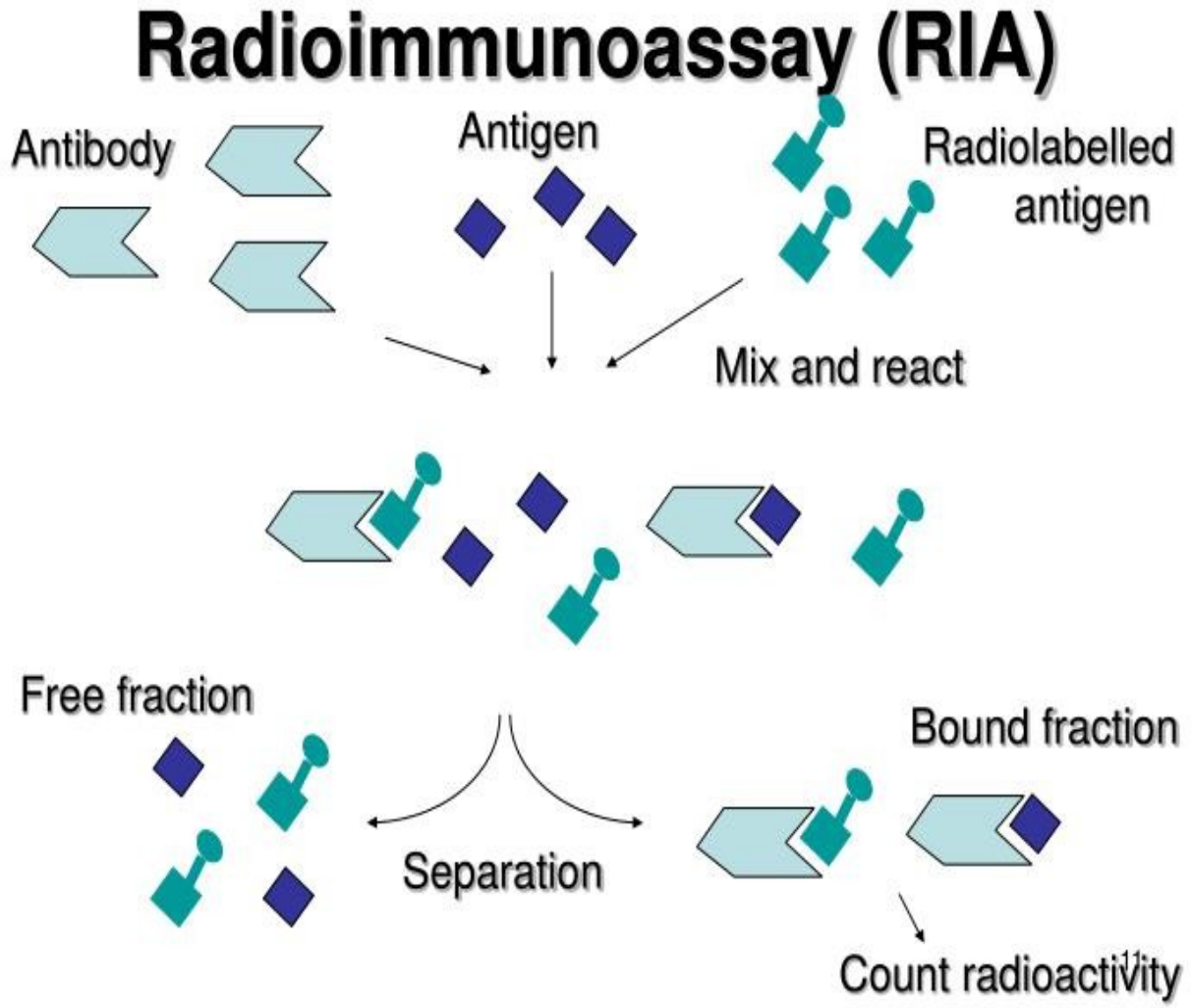
✓**Antigens are present during normal fetal life , tumor cells but not on normal adult tissue**

Carcinoemberyonic Ag (CEA) & Alpha fetoptn (

Carcinoembryonic antigen circulates at elevated levels in the serum of many patients with carcinoma of the colon, pancreas, breast, or liver. It is found in fetal gut, liver, and pancreas and in very small amounts in normal sera.

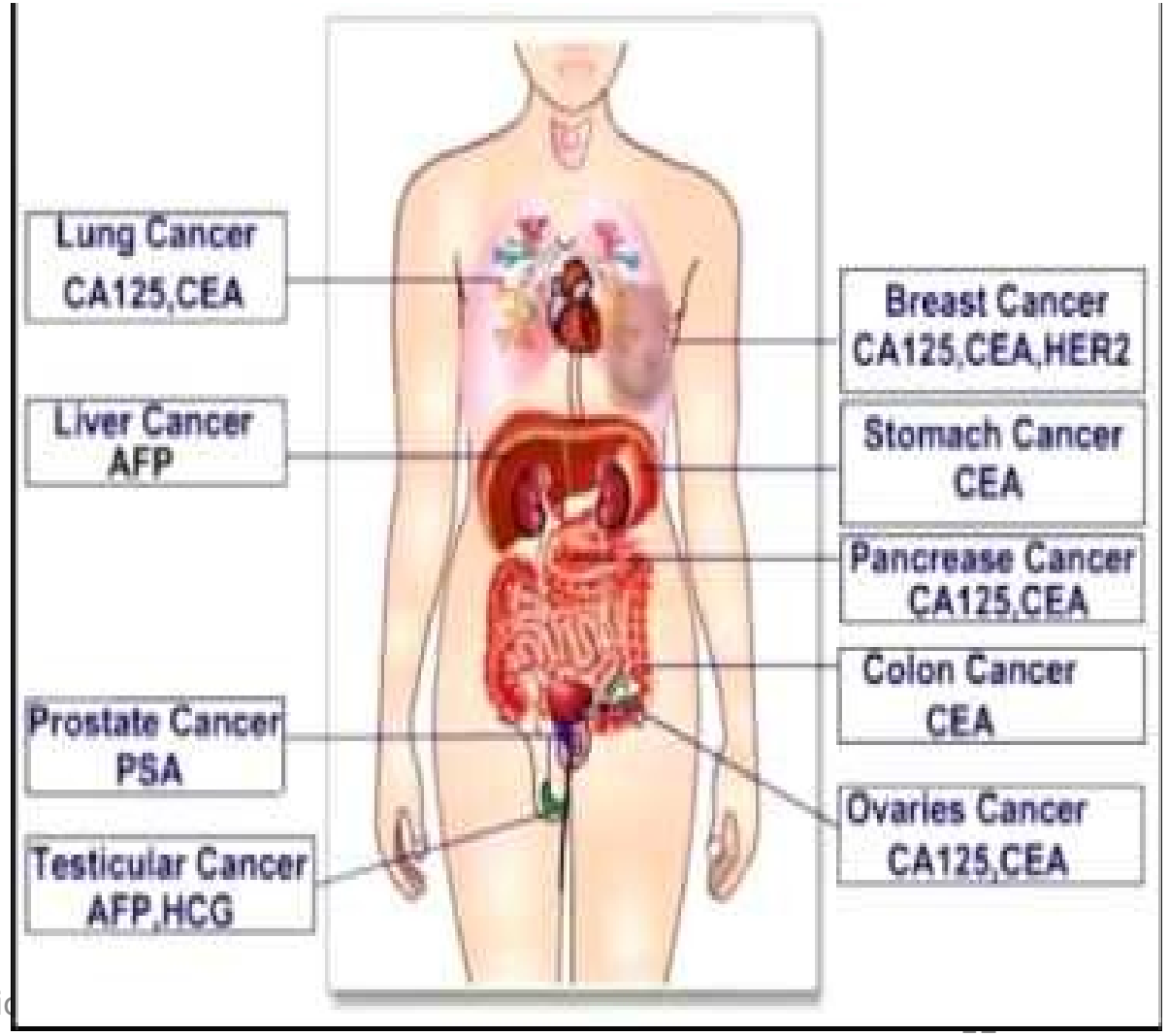
Carcinoemberyonic Ag (CEA)

- **Detection of CAE (by radioimmunoassay) is PROGNOSTIC i.e may be helpful in the FOLLOW UP of such tumors.**
- **If the level declines after surgery, it suggests that the tumor is not spreading.**



Alpha fetoprotein

- ✓**Alpha fetoprotein is present at elevated levels in the sera of hepatoma patients and is used as a marker for this disease.**
- **It is produced by fetal liver and is found in small amounts in some normal sera.**
- **It is nonspecific; it occurs in several other malignant and nonmalignant diseases.**



Quiz: Tumor antigens

Which of the following describes the behavior of tumor non-specific antigens?

a.Encoding genes are silenced in fetal life

b.Good prognostic m[illegible]

c.Products of mutated genes

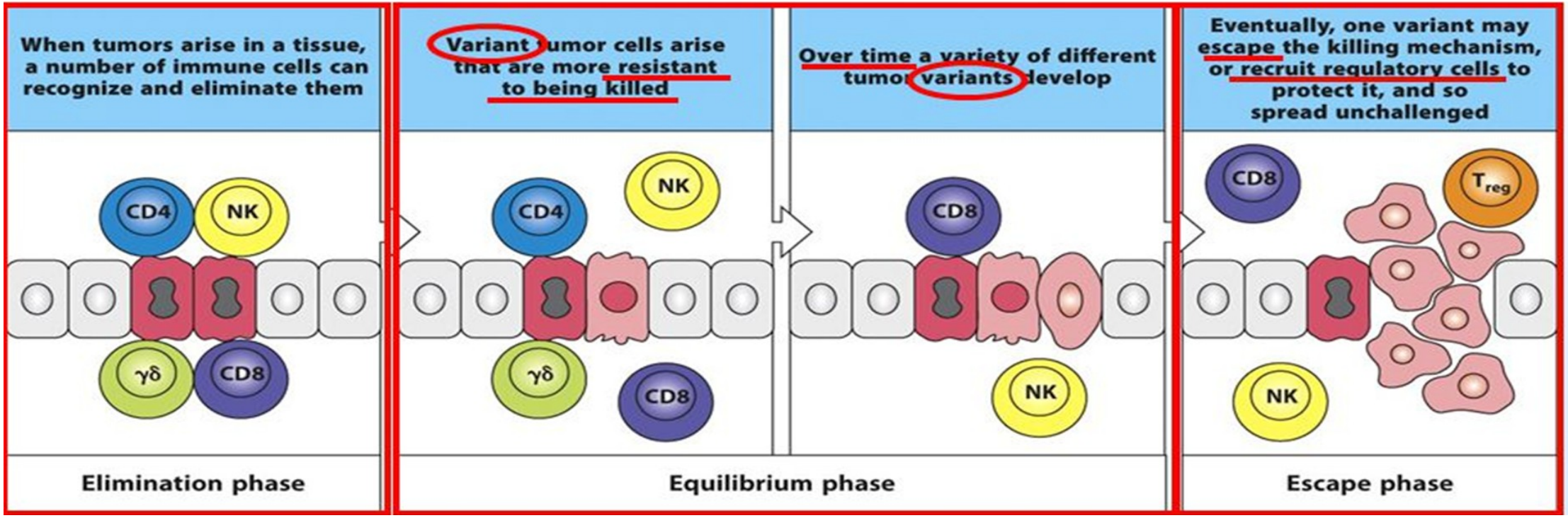
d.Differ according to causative oncogenic virus

e.They cross react one another

Immune Surveillance

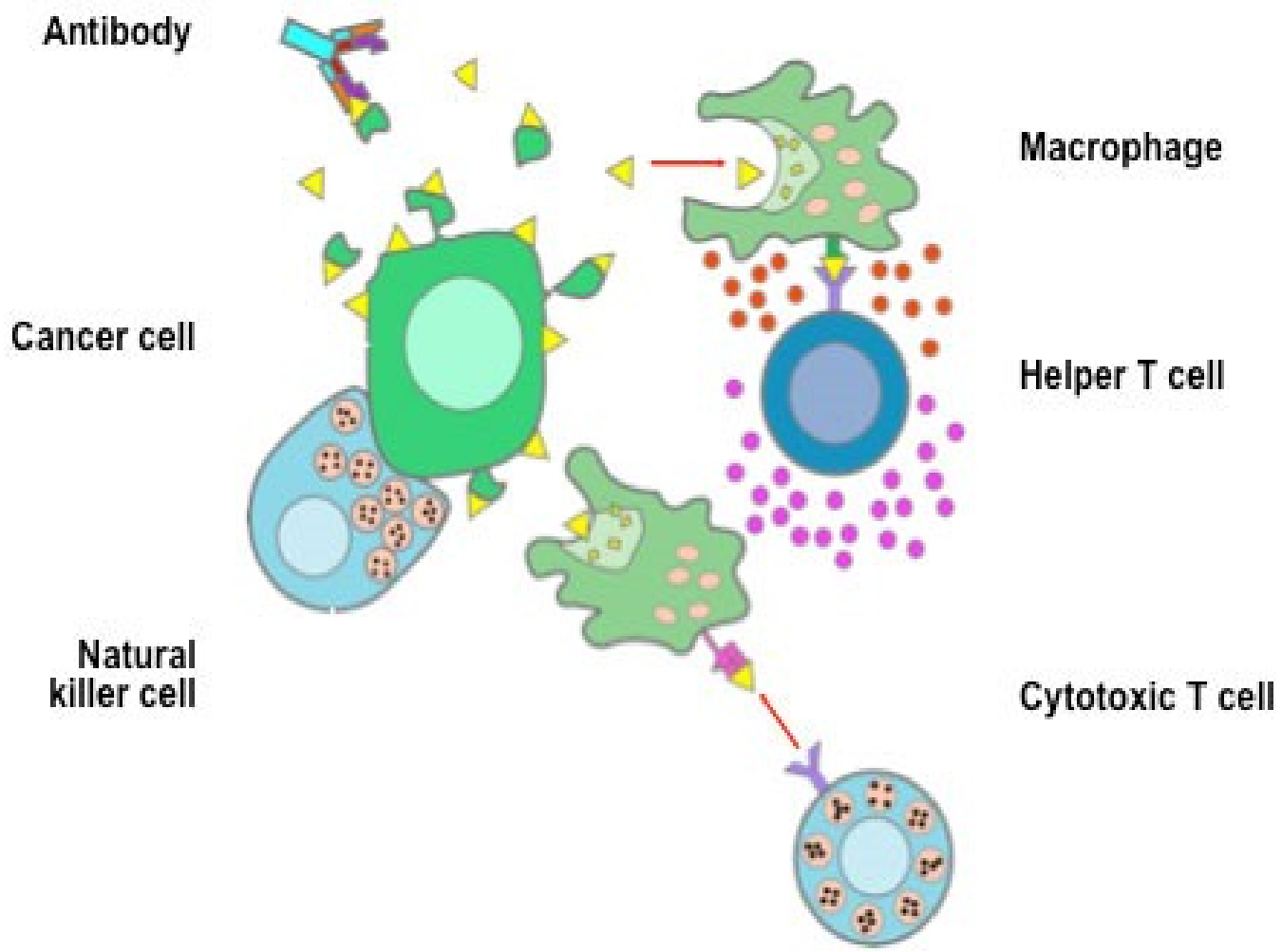
- **Immune surveillance of cancer: a physiologic function of the immune system is to recognize and destroy clones of transformed cells before they grow into tumors and to kill tumors after they are formed.**
- **The existence of immune surveillance has been demonstrated by the increased incidence of some types of tumors in immunocompromised experimental animals and humans.**

Immune Surveillance



Immune response against tumor cells

Both innate and adaptive immune responses can be detected in patients and experimental animals, and various immune mechanisms can kill tumor cells in vitro.



I.Innate IR:

A. Natural killer (NK) cells, which act without antibody

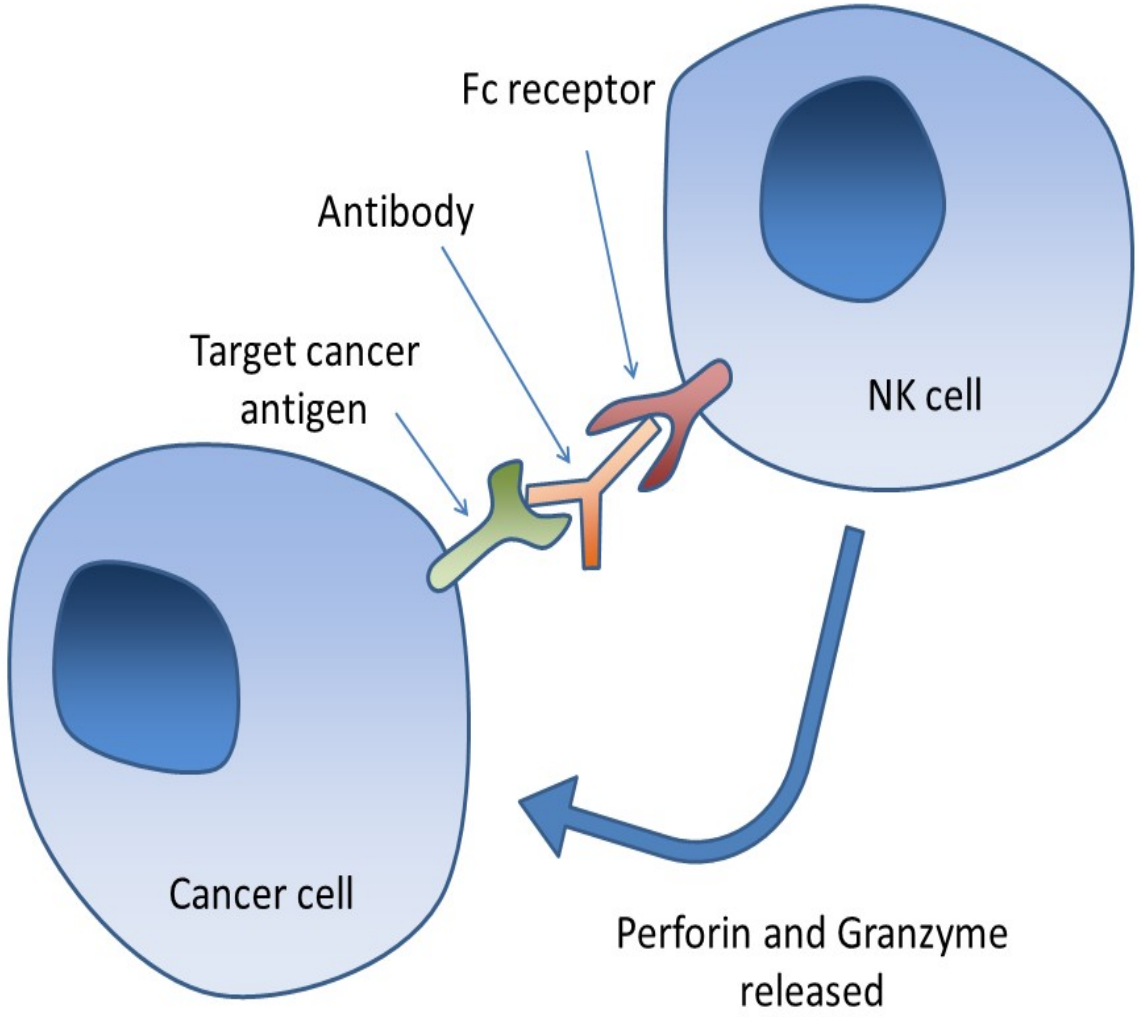
Immune response against tumor cells

II. Adaptive IR:

***A.Humoral: Antibodies*:**

Antibodies may kill tumor cells by:

- ✓**activating complement**
- ✓ **antibody-dependent cell-mediated cytotoxicity (ADCC), in which Fc receptor–bearing NK cells mediate the killing.**



Immune response against tumor cells

B. The cell-mediated immune responses that affect tumor cells in vitro include:

1. CD8 cytotoxic T lymphocyte

2. Activated macrophages: are capable of both inhibiting and promoting the growth and spread of cancers, depending on their activation state. Activation of macrophages by IFN-γ produced by tumor-specific T cells

Quiz: Immune Surveillance

- How can your immune system kill a tumor cell?

a.Immunoglobulins

b.T helper cells

c.T regulatory cells

d.NK cells

e.Antibody dependent cell mediated cytotoxicity

Tumor evasion of Immune response [Escape phenomenon

Tumor Ags related
nappropriate T cell stimulati
mmune Suppression by tumo
Host factors

Tumor evasion of Immune response

I. Tumor Ag related factors

A. -Hidden tumor Ag

Glycocalyx mol.

secreted by tumors

↓

Cover surface of tumor Ags

Tumors in immune privileged sites:

Eye, brain, testicles

↓

Grow without ⊕ IR

B.

Non cytotoxic Ab bind tumor Ag

↓

mask antigens from cytotoxic T lymphocytes

C. Lost tumor Ags

↓

Mutations or deletions in genes

encoding for tumor Ags

↓

Tumors stop expressing Ags

Tumor evasion of Immune response

II. Inappropriate T cell stimulation

EITHER : **Rare expression of B7 molecules on most tumors**

↓

Poor co-stimulation of CTLs

OR

↓ MHC class I on most tumor cells

↓

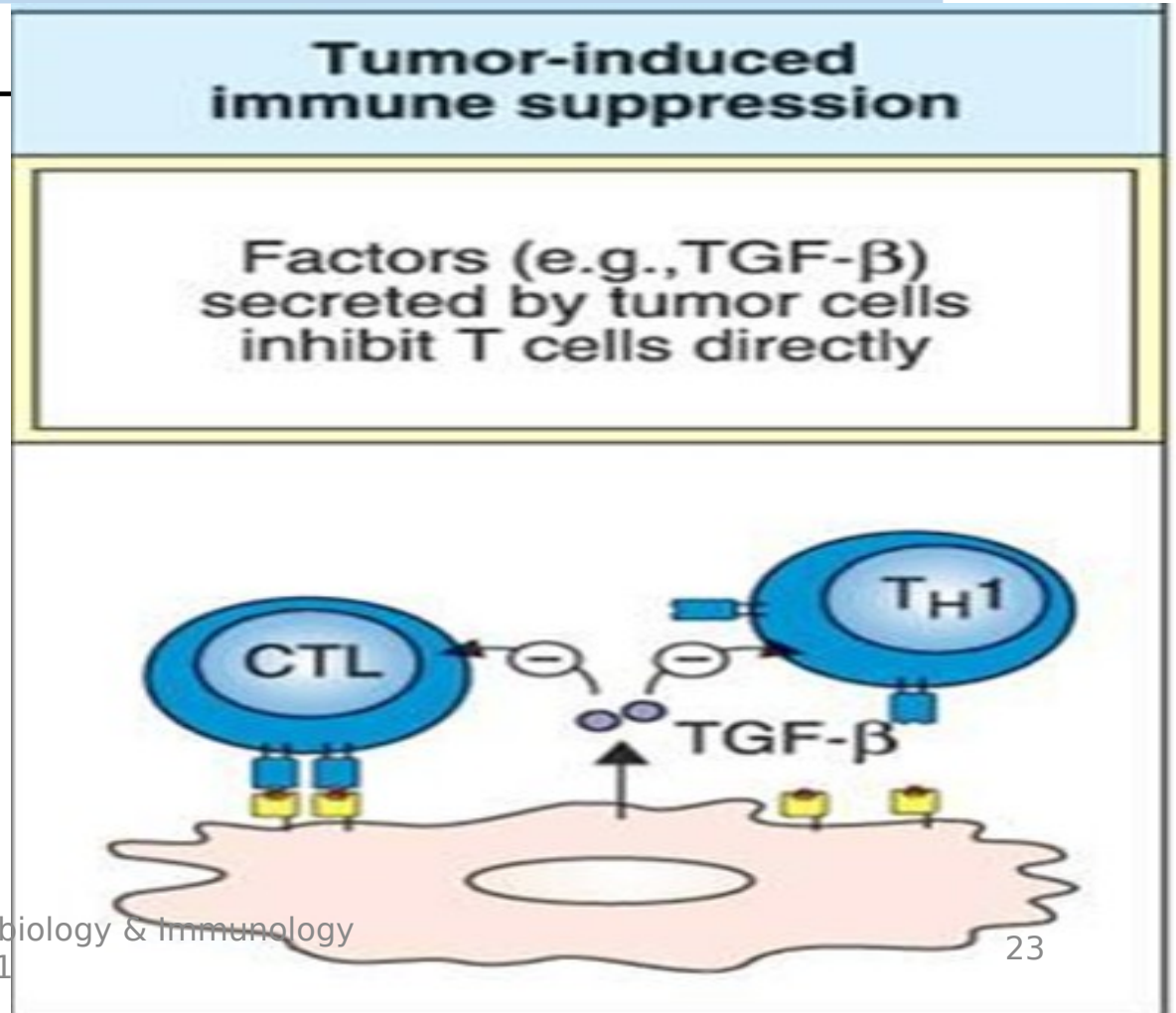
Not recognized by CTLs

Tumor evasion of Immune response

Direct Immune suppression by tumors

Secretion of TGFβ &IL10 → ⊖ MQ & lymphocytes

Induction of Treg cells → ⊖ T cell response to tumor Ags



Tumor evasion of Immune response

IV. Host related factors

↓**immunity** due to

Acquired Immune deficiency Syndrome (AIDS)

Immune Suppressive drugs

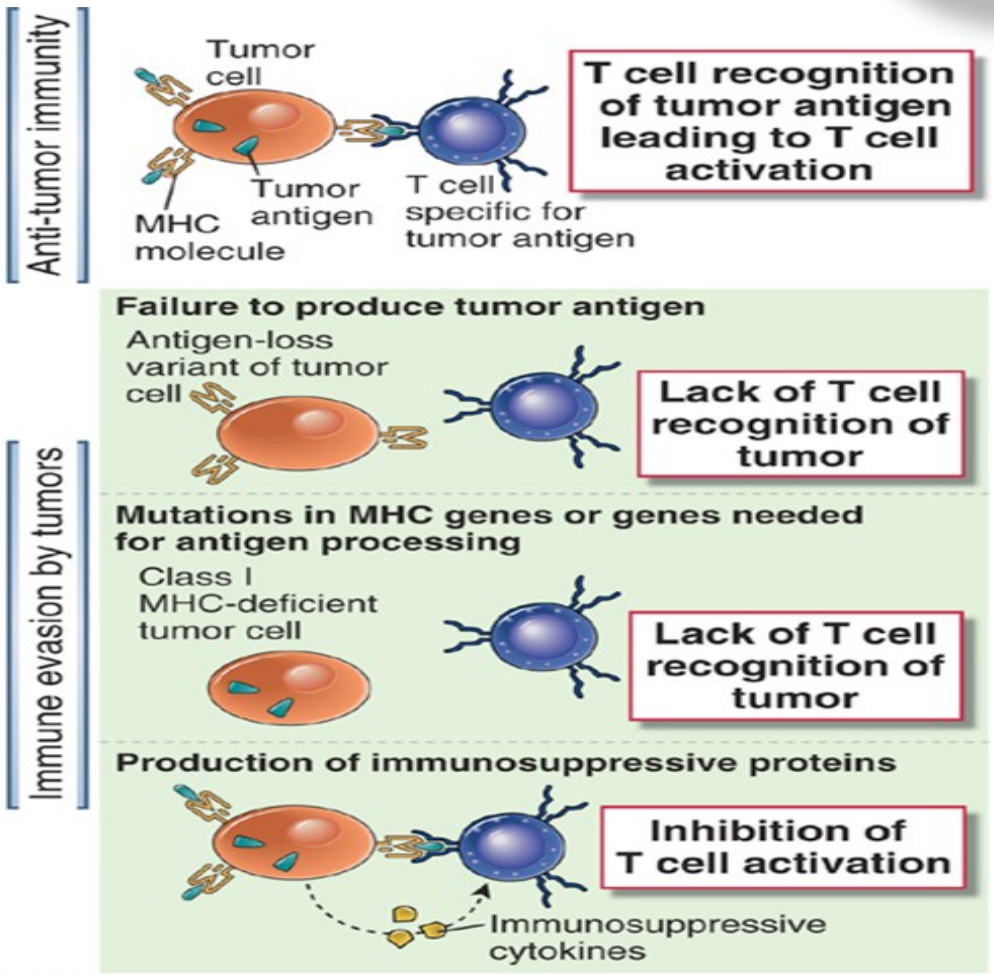
Treatment of autoimmune disease

Prevention of graft rejection

Extremes of age

Immature or exhausted Immune system

To sum up!!!



Abbas et al: Cellular and Molecular Immunology, 7e.


Break
Time

Tumor Immune therapy

I. **Non-specific stimulation of the immune system by the use of immunomodulators:** either bacterial products e.g. BCG, or eukaryotic cell products e.g. thymic hormones and cytokines (IL-2 and IFNs).

II. Active Immunization:

A.Using vaccines prepared from treated tumor cells or purified tumor antigens after reduction of tumor mass by surgery or radiotherapy.

Tumor Immune therapy

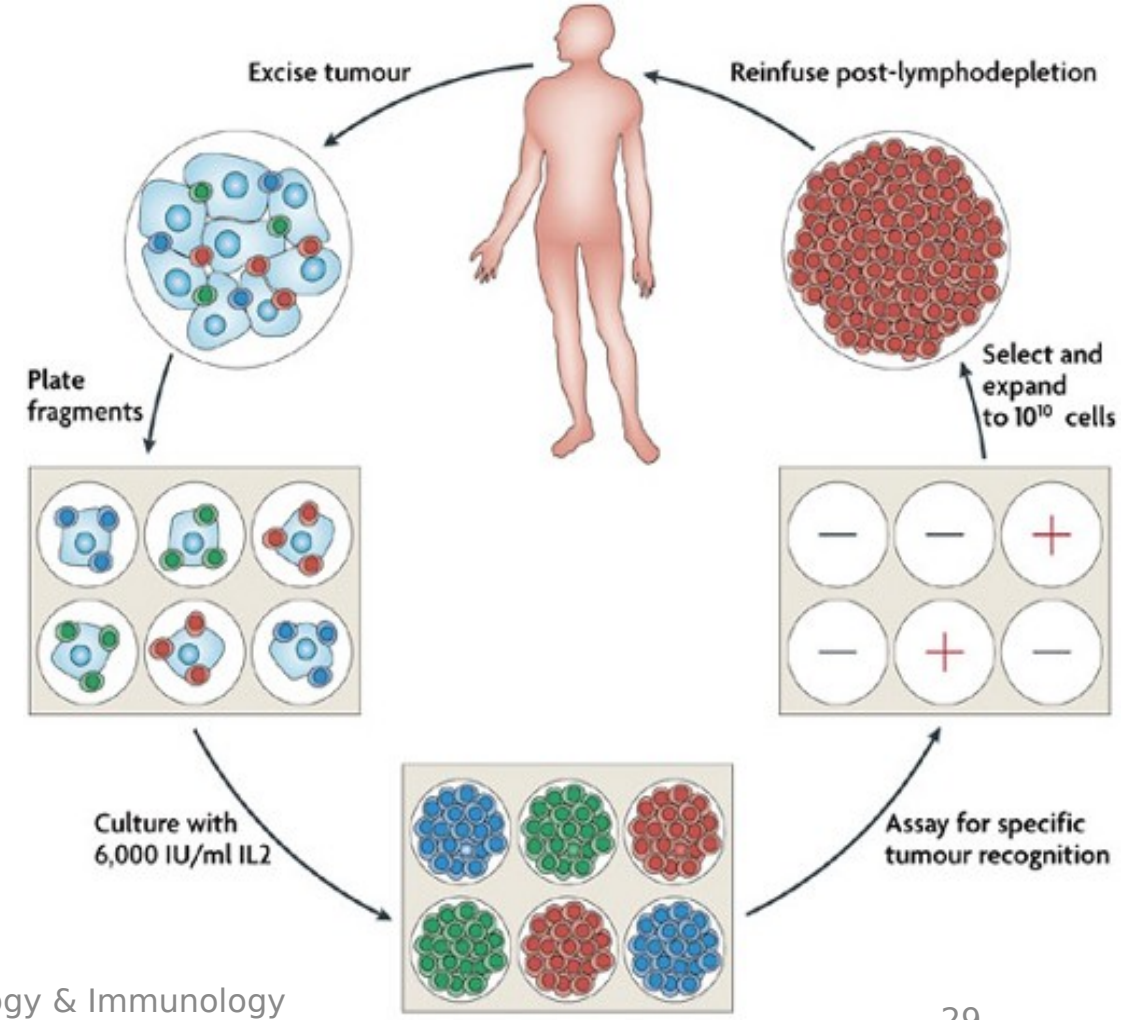
B. Immunization with DNA encoding foreign MHC Ags into the tumor leading to expression of alloantigen (foreign MHC) creating an immune response against both alloantigens and tumor antigens

III. Passive Immunotherapy : A. Adoptive cellular immunotherapy:

1. ***The use of tumor-infiltrating lymphocytes (TIL):*** **Some cancers are infiltrated by lymphocytes (NK cells and cytotoxic T cells) that seem likely to be trying to destroy the cancer cells.**

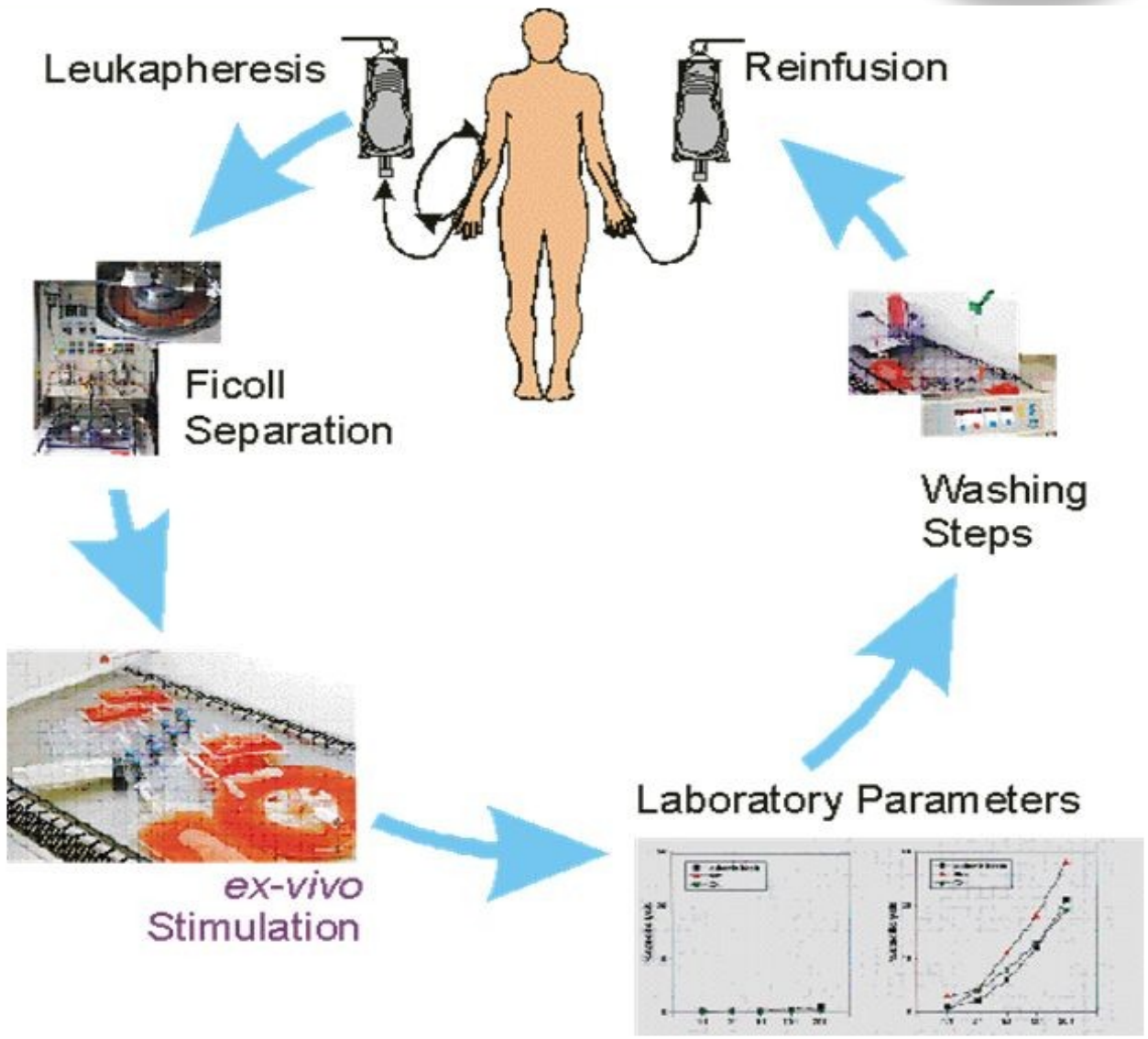
Immune modulators in tumor immune therapy

These lymphocytes are recovered from the surgically removed cancer, grown in cell culture until large numbers of cells are obtained, activated with interleukin-2, and returned to the patient in the expectation that the TIL will "home in" specifically on the cancer cells and kill them.



Tumor Immune therapy

2. *Lymphocytes activated by interleukin-2 (lymphokine-activated killer [LAK] cells)* may be useful in cancer immunotherapy.



Tumor Immune therapy

B. Therapeutic monoclonal antibodies:

1. Monoclonal antibodies directed against CTLA-4 (inhibitor of costimulatory response) enhance the immune response against tumors

2. Monoclonal antibodies directed against new surface antigens on malignant cells (e.g., B-cell lymphomas) can be useful in diagnosis.

Tumor Immune therapy

3. Monoclonal antibodies coupled to toxins, such as diphtheria toxin or ricin, a product of the Ricinus plant, can kill tumor cells in vitro and may be useful for cancer therapy prospectively.

IV. Genetic Manipulation of Tumor Cells:

By introduction of cytokine genes coding for IL-2, TNF, IFN-γ, GM-CSF or coding for costimulatory molecules e.g. B7.1 and B7.2.

Quiz: Immune evasion by tumor cells

How can inappropriate T cell stimulation play a role in immune evasion by tumor cells?

a.Rare expression of B7 molecules on most tumors

b.Massive co-stimulation of CTLs

c.Increased expression of MHC class I on most tumor cells

d.Poor expression of MHC II on all tumor cells

e.Masking antigens from cytotoxic T lymphocytes

1. Tumors develop new antigens on cells either specific or non specific
2. The immune system combat tumor via series of sequences summarized in the immune surveillance theory
3. Both humoral & cell mediated immune response are acting against tumors
4. Tumors exploit many mechanisms to escape the immune system armory
5. Immune therapy modalities are promising in tumor management

Suggested Text Books

1. ***Review of Medical Microbiology and Immunology, Warren Levinson Chapter 68 p. 1236: 1249***
2. ***Cellular and molecular Immunolgy , Abul Abbas & Lichtmann, 2015, Chapter 18 p.383:397***


THANK
YOU